

What is claimed is:

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A1
1. A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to said mammal a therapeutically-effective amount of a combination of a matrix metalloproteinase inhibitor and one or more antineoplastic agents, wherein said antineoplastic agents are selected from the group consisting of anastrozole, calcium carbonate, capecitabine, Cell Pathways CP-461, docetaxel, doxorubicin, fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, paclitaxel, raloxifene, retinoic acid, thiotepa, topotecan, toremifene, vinorelbine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone and eflornithine (DFMO).
2. The method of Claim 1 wherein the combination is administered in a sequential manner.
3. The method of Claim 1 wherein the combination is administered in a substantially simultaneous manner.
4. The method of Claim 1 wherein the antineoplastic agent is capecitabine.
5. The method of Claim 1 wherein the antineoplastic agent is Cell Pathways CP-461.
6. The method of Claim 1 wherein the antineoplastic agent is docetaxel.
7. The method of Claim 1 wherein the antineoplastic agent is doxorubicin.
8. The method of Claim 1 wherein the antineoplastic agent is fluoxymestrine.

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9. The method of Claim 1 wherein the antineoplastic agent is gemcitabine.

10. The method of Claim 1 wherein the antineoplastic agent is goserelin.

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5 11. The method of Claim 1 wherein the antineoplastic agent is irinotecan.

12. The method of Claim 1 wherein the antineoplastic agent is ketoconazole.

10 13. The method of Claim 1 wherein the antineoplastic agent is letrozol.

14. The method of Claim 1 wherein the antineoplastic agent is leucovorin.

15 15. The method of Claim 1 wherein the antineoplastic agent is levamisole.

16. The method of Claim 1 wherein the antineoplastic agent is megestrol.

17. The method of Claim 1 wherein the antineoplastic agent is paclitaxel.

20 18. The method of Claim 1 wherein the antineoplastic agent is raloxifene.

19. The method of Claim 1 wherein the antineoplastic agent is retinoic acid.

20. The method of Claim 1 wherein the antineoplastic agent is thiotepa.

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Cont

25 21. The method of Claim 1 wherein the antineoplastic agent is topotecan.

22. The method of Claim 1 wherein the antineoplastic agent is toremifene.

30 23. The method of Claim 1 wherein the antineoplastic agent is vinorelbine.

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24. The method of Claim 1 wherein the antineoplastic agent is selenium (selenomethionine).

25. The method of Claim 1 wherein the antineoplastic agent is ursodeoxycholic acid.

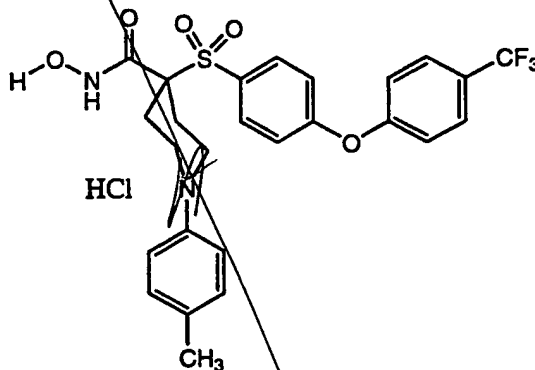
5 26. The method of Claim 1 wherein the antineoplastic agent is sulindac sulfone.

27. The method of Claim 1 wherein the antineoplastic agent is eflornithine (DFMO).

10 28. The method of Claim 1 wherein the neoplasia is selected from the group consisting of lung cancer, breast cancer, gastrointestinal cancer, bladder cancer, head and neck cancer and cervical cancer.

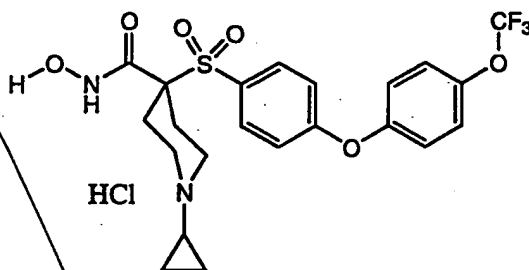
15 29. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

1)



20 N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

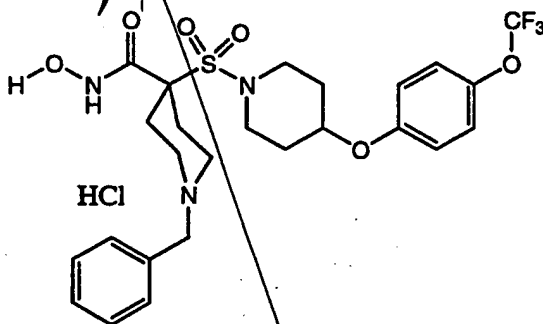
2)



1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

5

3)

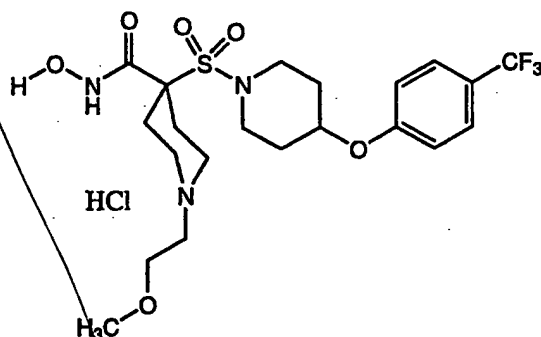


N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidiny]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

10

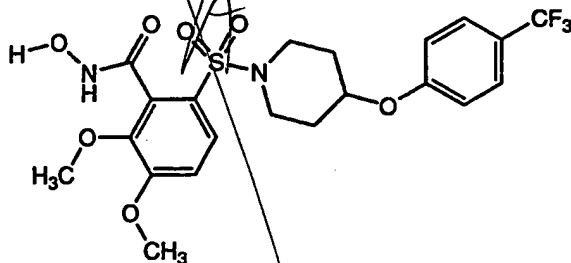
-227-

4)



N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

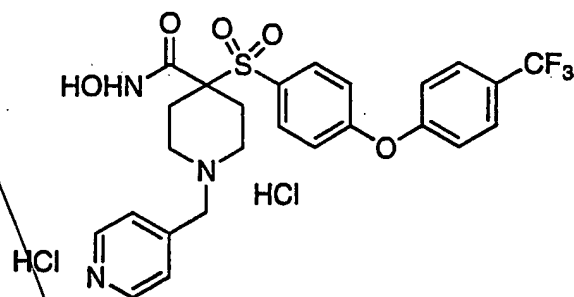
5)



N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide,

10

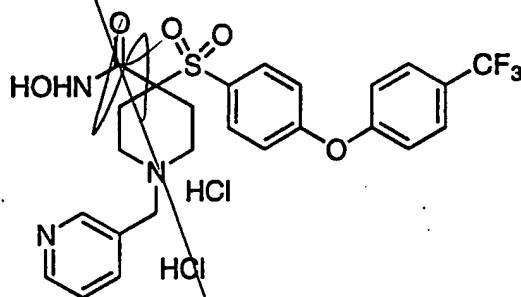
6)



N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

5

7)

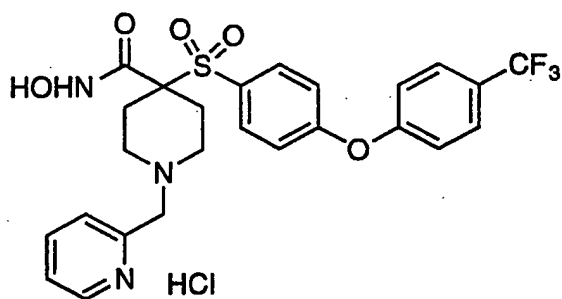


N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

10

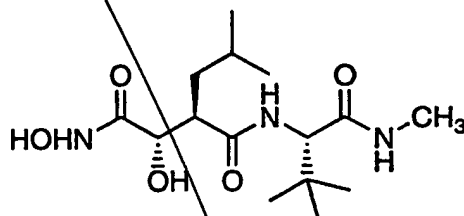
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8)



N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

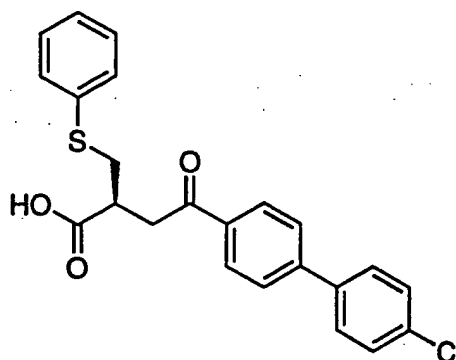
9)



British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-,

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10)

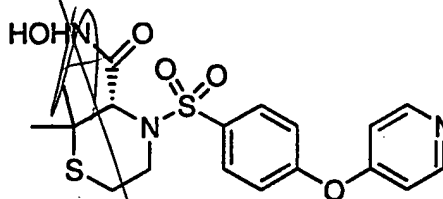


Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-  
iphenyl]-4-yl)oxy]-2-

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[(phenylthio)methyl]butanoic acid,

11)



Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2  
dimethyl-4-[[4-(4-  
pyridinyloxy)phenyl]sulfonyl] 3-  
thiomorpholinecarboxamide,

10

12) CollaGenex Pharmaceuticals CMT-3 (Metastat),  
6-demethyl-6-deoxy-4-

15

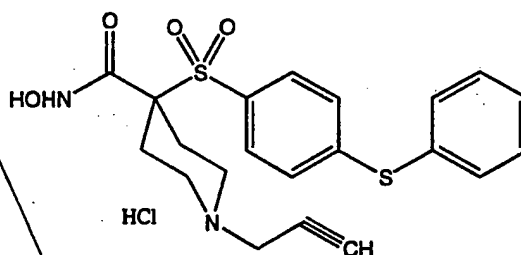
dedimethylaminotetracycline,

13) Chiroscience D-2163, 2- [1S- ([ (2R,S)-  
acetylmercapto- 5- phthalimido]pentanoyl- L-  
leucyl)amino- 3- methylbutyl]imidazole,



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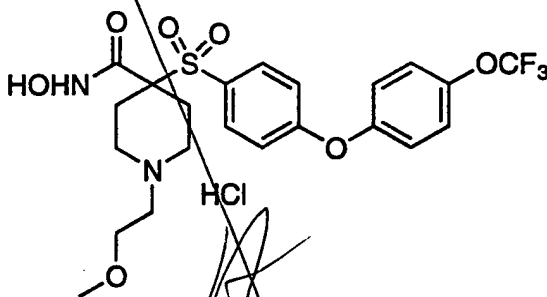
14)



N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-  
1-(2-propynyl)-4-piperidinecarboxamide  
monohydrochloride,

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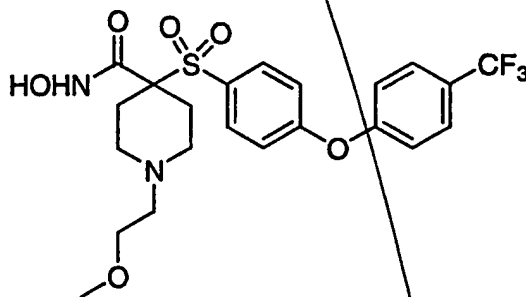
15)



N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-  
(trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4-  
piperidinecarboxamide monohydrochloride,

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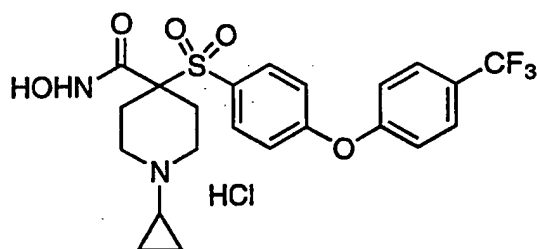
16)



N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-  
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-  
piperidinecarboxamide,

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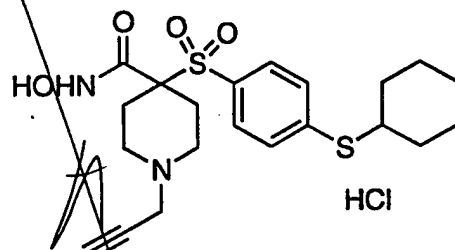
17)



1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

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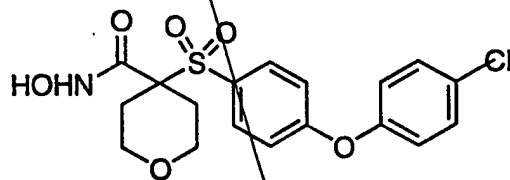
18)



4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

10

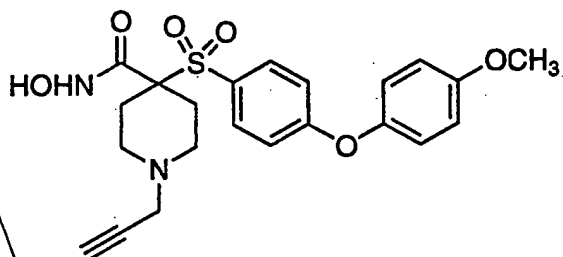
19)



4-[[4-(4-chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide,

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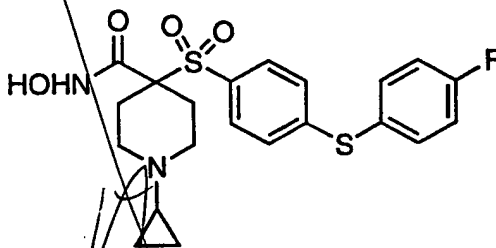
20)



N-hydroxy-4-[[4-(4-methoxyphenoxy)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide,

5

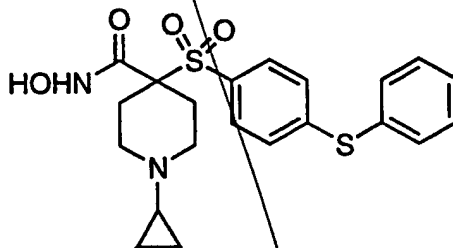
21)



1-cyclopropyl-4-[[4-[(4-fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide,

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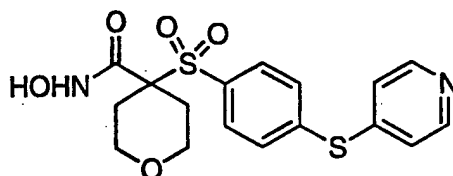
22)



1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide,

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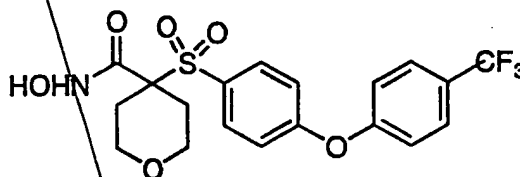
23)



tetrahydro-N-hydroxy-4-[[4-(4-  
pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-  
carboxamide, and

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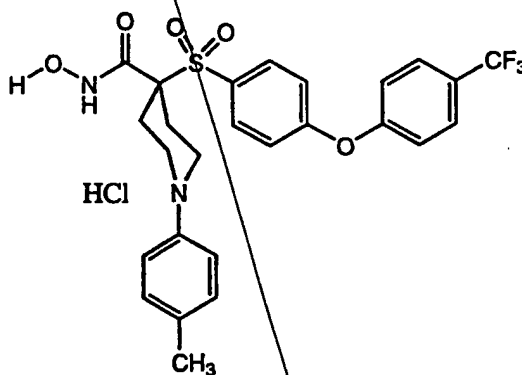
24)



tetrahydro-N-hydroxy-4-[[4-[4-  
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2H-  
pyran-4-carboxamide.

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30. The method of Claim 1 wherein the matrix  
metalloproteinase inhibitor is

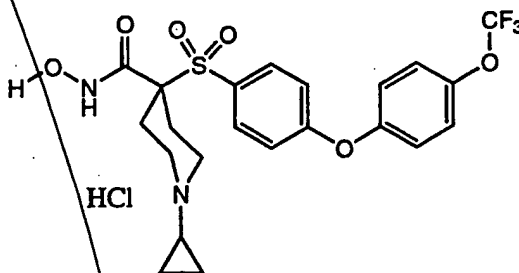


N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-  
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-  
piperidinecarboxamide monohydrochloride.

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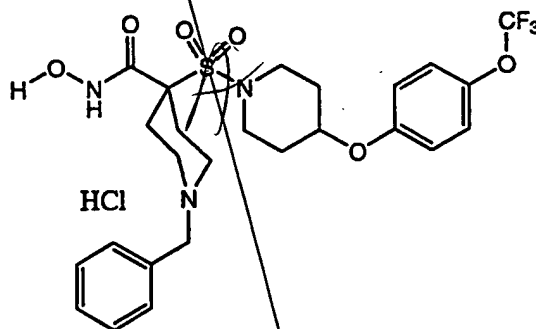
31. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is



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1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

32. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

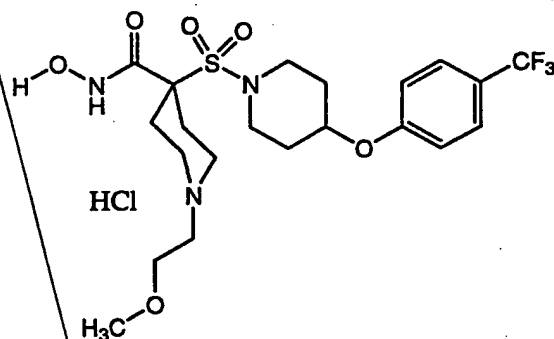


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N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

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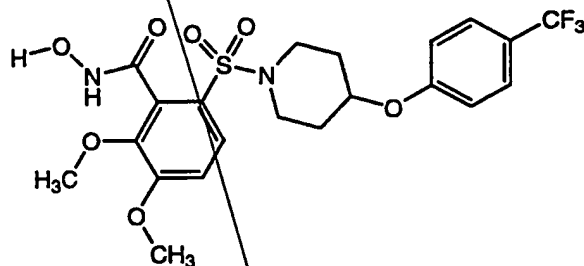
33. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is



5 N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

34. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

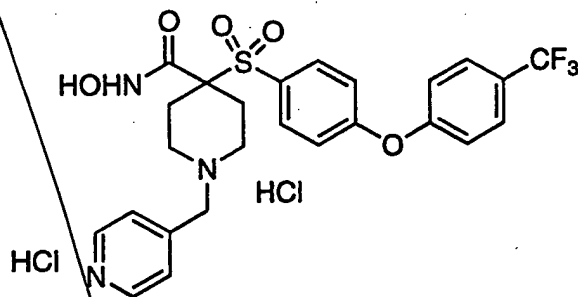
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N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide.

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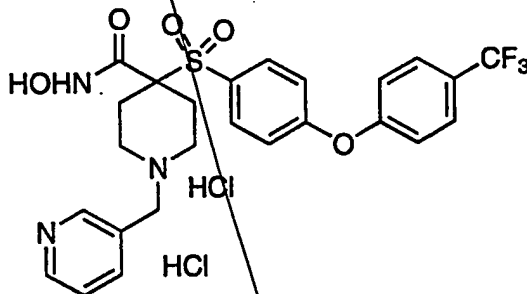
35. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is



5 N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

36. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

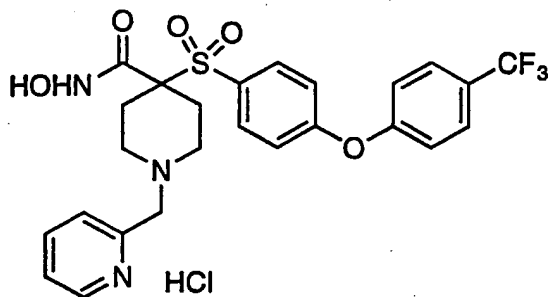
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N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

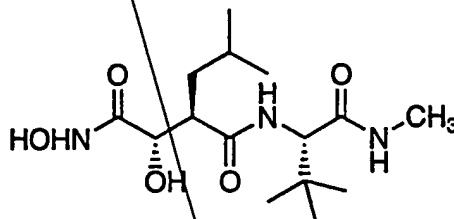
37. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is



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N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

38. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is

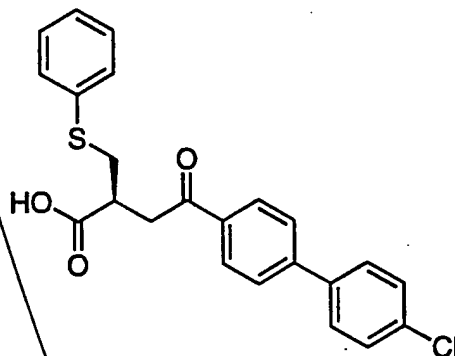


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British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-).

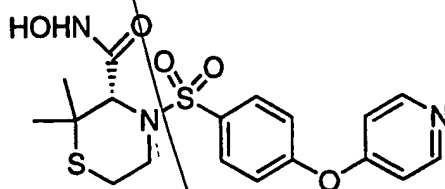


39. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is



5 Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-  
iphenyl]- 4-yl)oxy]-2-  
[(phenylthio)methyl]butanoic acid.

40. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is



15 Agouron Pharmaceuticals AG-3340, N-hydroxy-  
2,2-dimethyl-4-[[4-(4-  
pyridinyloxy)phenyl]sulfonyl]- 3-  
thiomorpholinecarboxamide.

41. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is CollaGenex  
Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-  
20 dedimethylaminotetracycline.

42. The method of Claim 1 wherein the matrix metalloproteinase inhibitor is Chiroscience D-2163, 2-[1S- ([[(2R,S)- acetylmercapto- 5- phthalimido]pentanoyl-L- leucyl)amino- 3- methylbutyl]imidazole.

- 5 43. The method of Claim 1 wherein the neoplasia is selected from the group consisting of acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma, 10 basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial 15 hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, hemangioblastomas, hemangioendothelioma, hemangiomas, 20 hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant 25 melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, 30 osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors,

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cont

B' cont  
plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

- Sub A2  
10 44. A method for treating or preventing a neoplasia disorder in a mammal in need of such treatment or prevention, which method comprises administering to said mammal a therapeutically-effective amount of a combination of radiation therapy, a matrix  
15 metalloproteinase inhibitor, and one or more antineoplastic agent, wherein said antineoplastic agents are selected from the group consisting of anastrozole, calcium carbonate, capecitabine, Cell Pathways CP-461, docetaxel, doxorubicin, fluoxymestrine, gemcitabine,  
20 goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, paclitaxel, raloxifene, retinoic acid, thiotepa, topotecan, toremifene, vinorelbine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone and eflornithine  
25 (DFMO).

B' cont  
45. The method of Claim 44 wherein the combination is administered in a sequential manner.

46. The method of Claim 44 wherein the combination is administered in a substantially simultaneous manner.

- 30 47. The method of Claim 44 wherein the antineoplastic agent is capecitabine.

48. The method of Claim 44 wherein the antineoplastic agent is Cell Pathways CP-461.

49. The method of Claim 44 wherein the antineoplastic agent is docetaxel.

5 50. The method of Claim 44 wherein the antineoplastic agent is doxorubicin.

51. The method of Claim 44 wherein the antineoplastic agent is fluoxymestrine.

52. The method of Claim 44 wherein the  
10 antineoplastic agent is gemcitabine.

53. The method of Claim 44 wherein the antineoplastic agent is goserelin.

54. The method of Claim 44 wherein the antineoplastic agent is irinotecan.

15 55. The method of Claim 44 wherein the antineoplastic agent is ketoconazole.

56. The method of Claim 44 wherein the antineoplastic agent is letrozol.

57. The method of Claim 44 wherein the  
20 antineoplastic agent is leucovorin.

58. The method of Claim 44 wherein the antineoplastic agent is levamisole.

59. The method of Claim 44 wherein the antineoplastic agent is megestrol.

25 60. The method of Claim 44 wherein the antineoplastic agent is paclitaxel.

61. The method of Claim 44 wherein the antineoplastic agent is raloxifene.

62. The method of Claim 44 wherein the  
30 antineoplastic agent is retinoic acid.

B1  
cont

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63. The method of Claim 44 wherein the antineoplastic agent is thiotepa.

64. The method of Claim 44 wherein the antineoplastic agent is topotecan.

5 65. The method of Claim 44 wherein the antineoplastic agent is toremifene.

66. The method of Claim 44 wherein the antineoplastic agent is vinorelbine.

67. The method of Claim 44 wherein the  
10 antineoplastic agent is selenium (selenomethionine).

68. The method of Claim 44 wherein the antineoplastic agent is ursodeoxycholic acid.

69. The method of Claim 44 wherein the antineoplastic agent is sulindac sulfone.

15 70. The method of Claim 44 wherein the antineoplastic agent is eflornithine (DFMO).

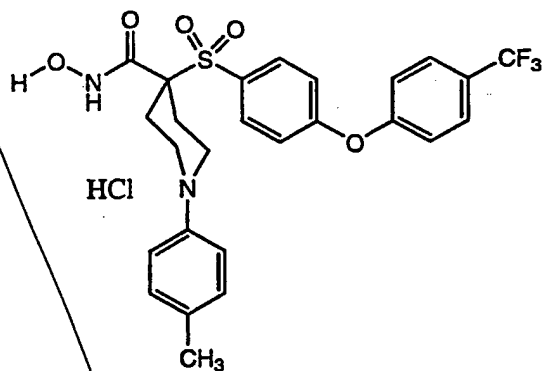
71. The method of Claim 44 wherein the neoplasia is selected from the group consisting of lung cancer, breast cancer, gastrointestinal cancer, bladder cancer,  
20 head and neck cancer and cervical cancer.

72. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

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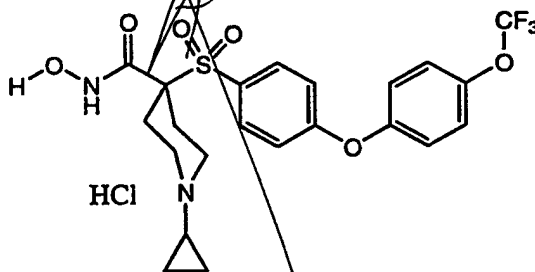
1)



N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

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2)

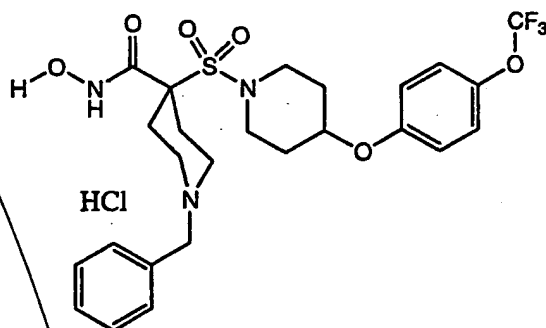


1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

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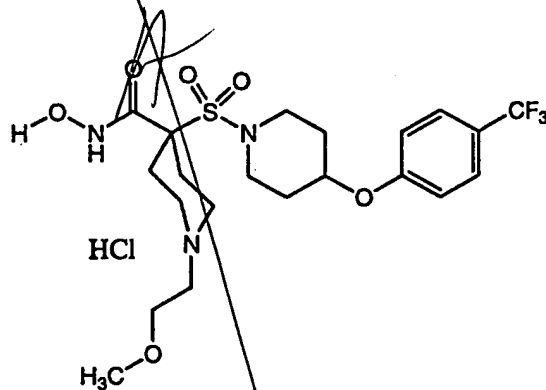
-245-

3)



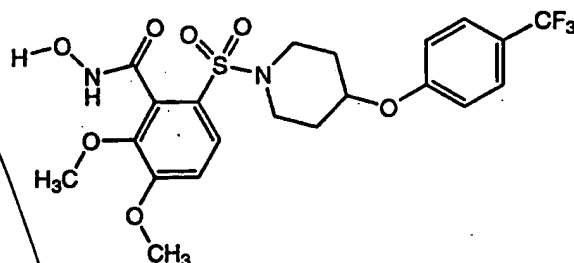
N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

4)



N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

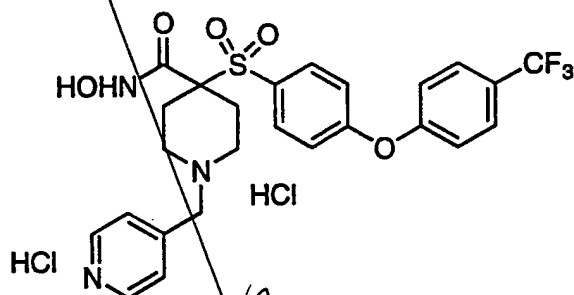
5)



N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide,

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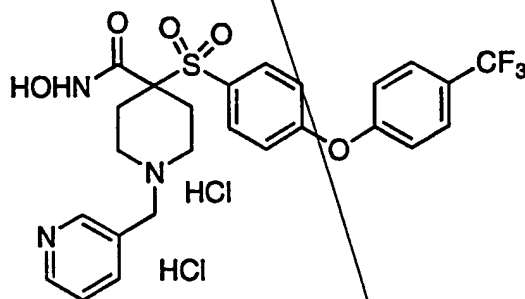
6)



N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

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7)



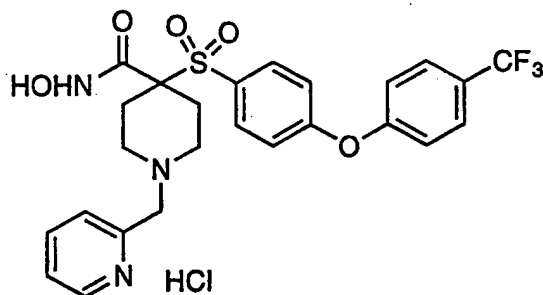
N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

15



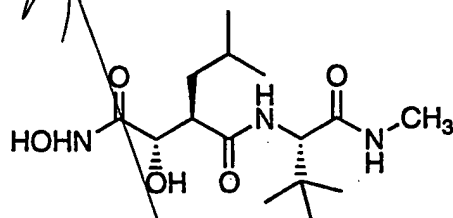
-247-

8)



N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

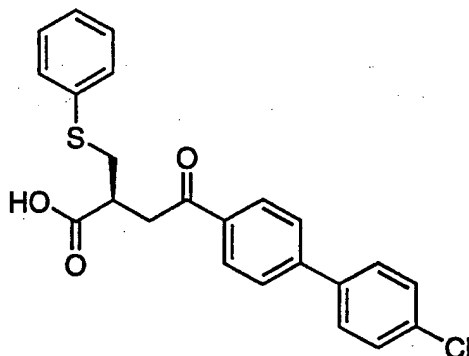
9)



British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-,

10

10)

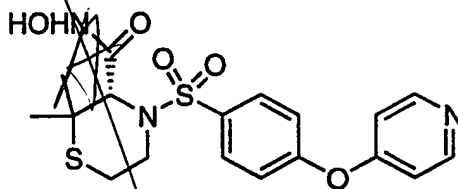


Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-  
iphenyl]-4-yl)oxy]-2-

5

[(phenylthio)methyl]butanoic acid,

11)



Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2  
dimethyl-4-[[4-(4-  
pyridinyloxy)phenyl]sulfonyl] 3-  
thiomorpholinecarboxamide,

10

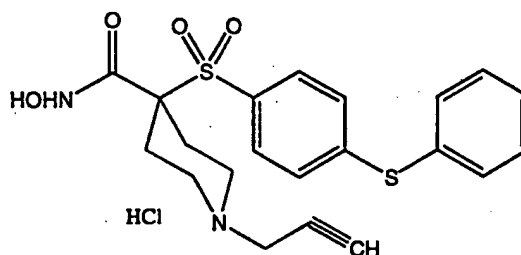
12) CollaGenex Pharmaceuticals CMT-3 (Metastat),  
6-demethyl-6-deoxy-4-

15

dedimethylaminotetracycline,

13) Chiroscience D-2163, 2- [1S- ((2R,S)-  
acetylmercapto- 5- phthalimido]pentanoyl- L-  
leucyl)amino- 3- methylbutyl]imidazole,

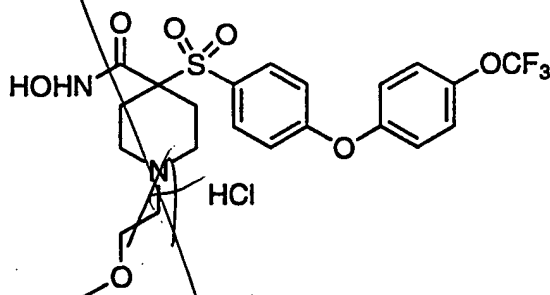
14)



N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-  
1-(2-propynyl)-4-piperidinecarboxamide  
monohydrochloride,

5

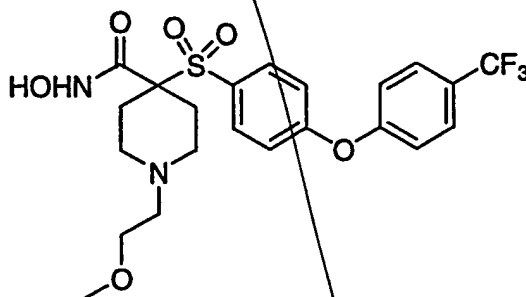
15)



N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-  
(trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4-  
piperidinecarboxamide monohydrochloride,

10

16)

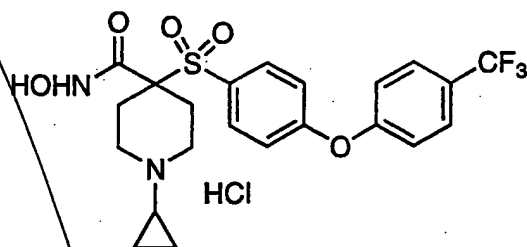


N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-  
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-  
piperidinecarboxamide,

15

-250-

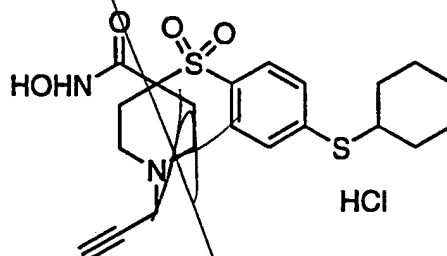
17)



1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

5

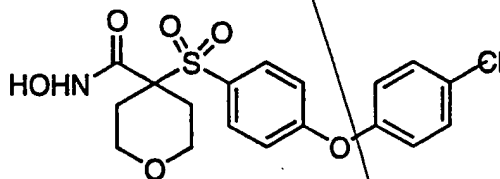
18)



4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

10

19)

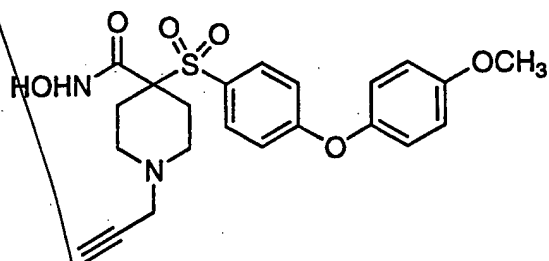


4-[[4-(4-chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide,

15

-251-

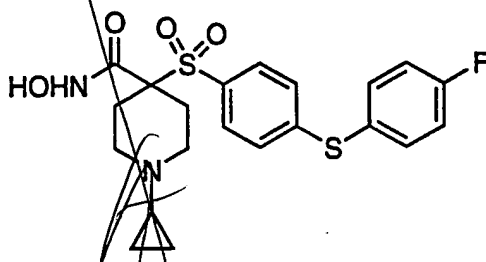
20)



N-hydroxy-4-[[4-(4-methoxyphenoxy)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide,

5

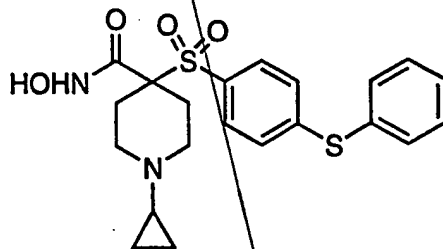
21)



1-cyclopropyl-4-[[4-[(4-fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide,

10

22)

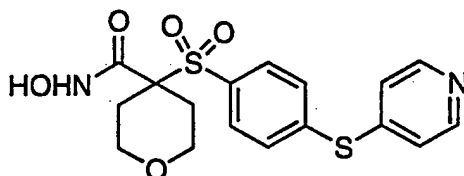


1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide,

15

-252-

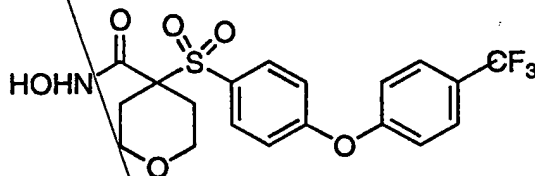
23)



tetrahydro-N-hydroxy-4-[[4-(4-  
pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-  
carboxamide, and

5

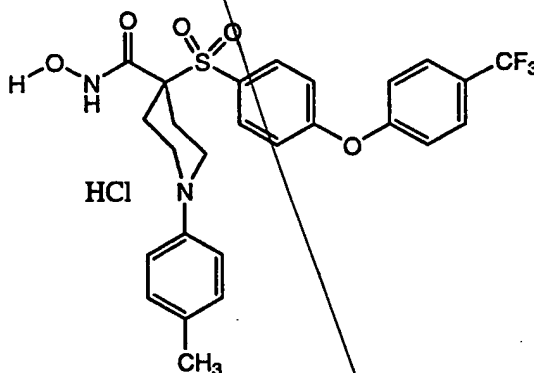
24)



tetrahydro-N-hydroxy-4-[[4-[4-  
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2H-  
pyran-4-carboxamide.

10

73. The method of Claim 44 wherein the matrix  
metalloproteinase inhibitor is

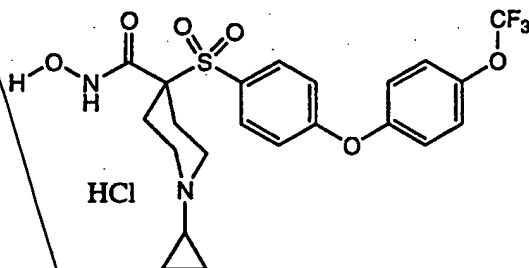


N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-  
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-  
piperidinecarboxamide monohydrochloride.

15

-253-

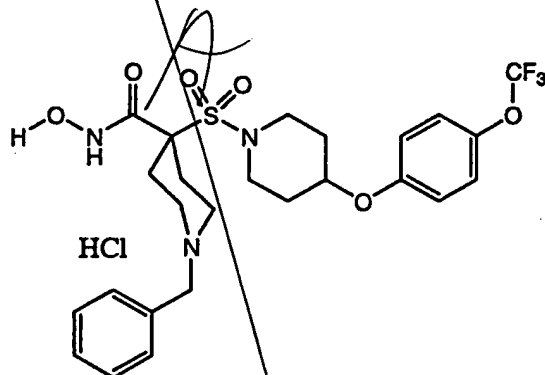
74. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is



5

1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

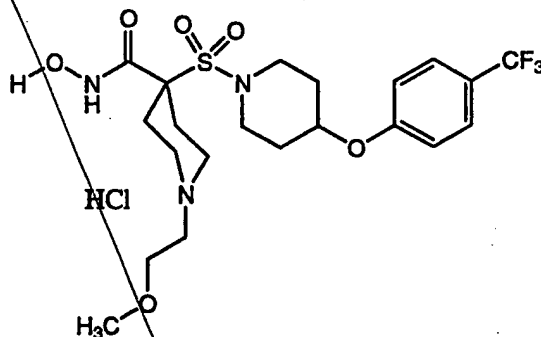
75. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is



10

N-hydroxy-1-(benzyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

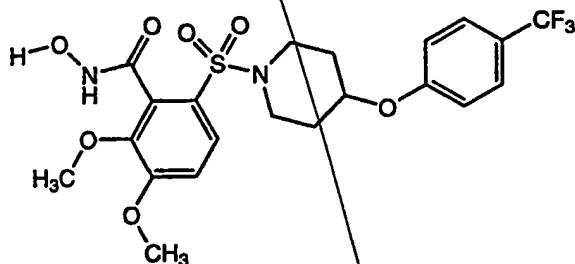
76. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is



5 N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

77. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is

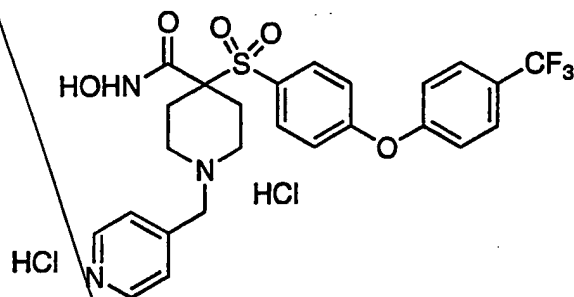
10



N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide.

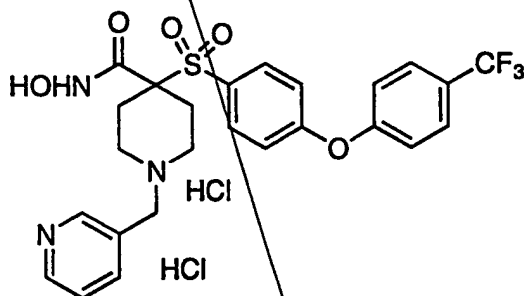


78. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is



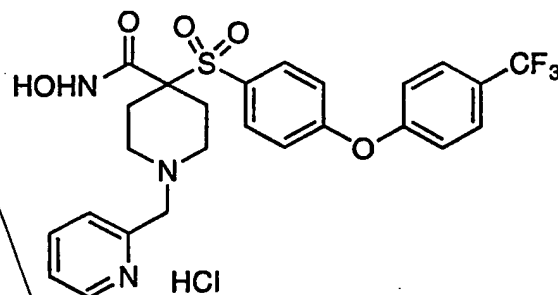
5 N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

79. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is



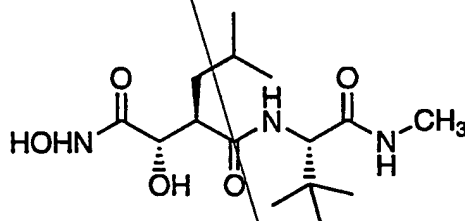
15 N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

80. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is



N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

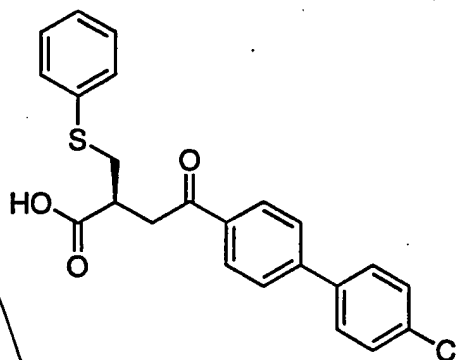
81. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is



British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-).

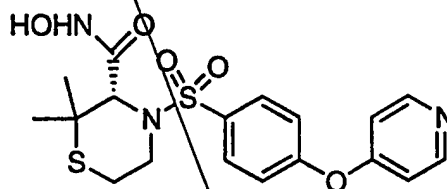
-257-

82. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is



5 Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-iphenyl]-4-yl)oxy]-2-[(phenylthio)methyl]butanoic acid.

83. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is



10 Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2-dimethyl-4-[[4-(4-pyridinyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxamide.

84. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is CollaGenex Pharmaceuticals ~~CMT-3~~ (Metastat), 6-demethyl-6-deoxy-4-  
5 dedimethylaminotetracycline.

85. The method of Claim 44 wherein the matrix metalloproteinase inhibitor is Chiroscience D-2163, 2-[1S- ((2R,S)- acetylmercapto- 5- phthalimido]pentanoyl-L-leucyl)amino- 3- methylbutyl]imidazole.

10 86. The method of Claim 44 wherein the neoplasia is selected from the group consisting of acral  
lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin  
15 gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor,  
20 endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, hemangioblastomas, hemangioendothelioma,  
25 hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant  
30 melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial,

B1  
cont

B1  
cont

metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor.

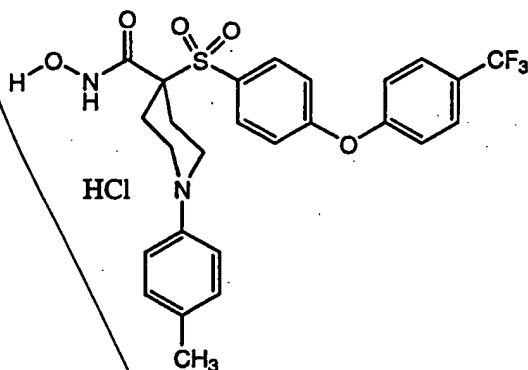
87. A combination comprising a matrix metalloproteinase inhibitor and one or more antineoplastic agents, wherein said antineoplastic agents are selected from the group consisting of anastrozole, calcium carbonate, capecitabine, Cell Pathways CP-461, docetaxel, doxorubicin, fluoxymestrine, gemcitabine, goserelin, irinotecan, ketoconazole, letrozol, leucovorin, levamisole, megestrol, paclitaxel, raloxifene, retinoic acid, thiotepa, topotecan, toremifene, vinorelbine, selenium (selenomethionine), ursodeoxycholic acid, sulindac sulfone and eflornithine (DFMO).

88. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is selected from compounds, and their pharmaceutically acceptable salts thereof, of the group consisting of:

1)

Sub  
A3

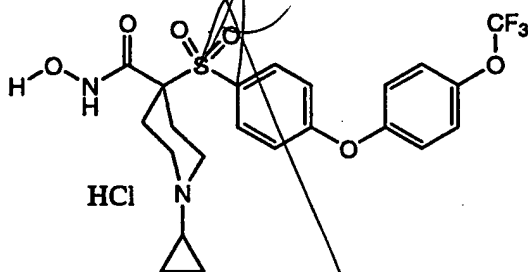
-260-



N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

5

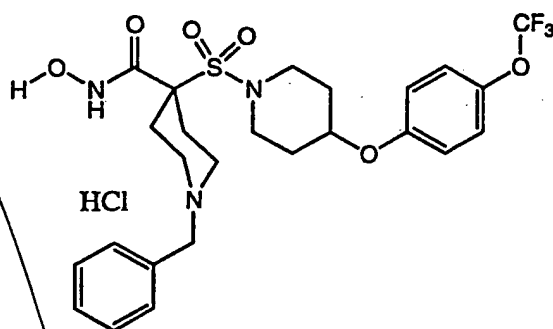
2)



1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

-261-

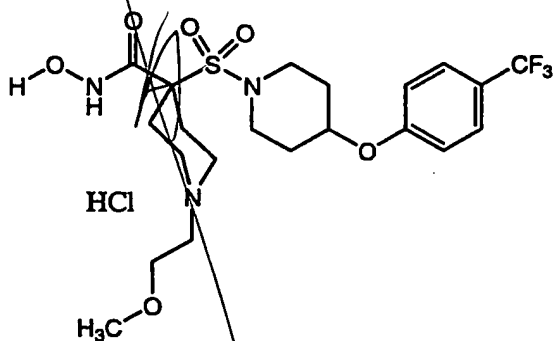
3)



N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

5

4)

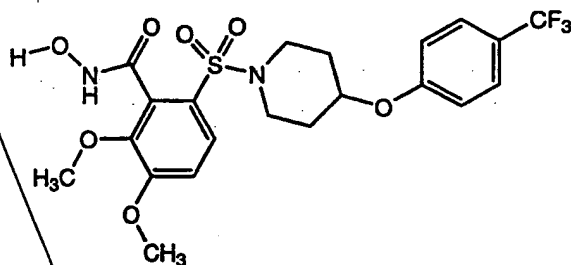


N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

10

-262-

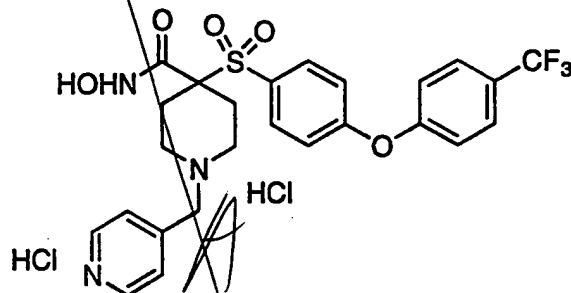
5)



N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide,

5

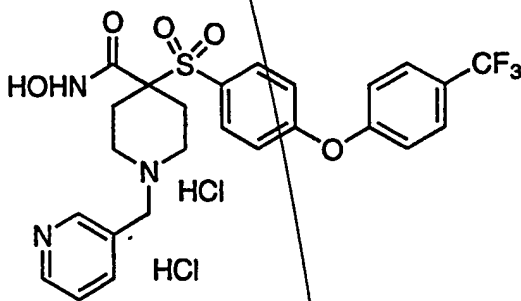
6)



N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

10

7)



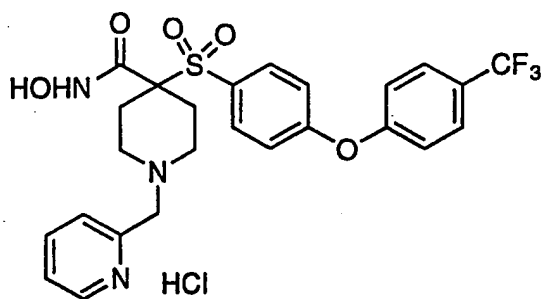
N-hydroxy-1-(3-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride,

15



-263-

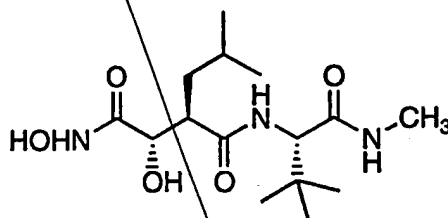
8)



5

N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-(4-(trifluoromethyl)phenoxy)phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

9)

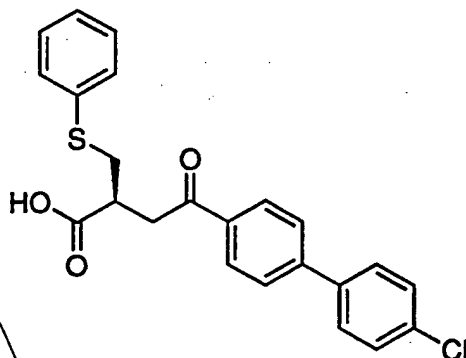


10

British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3-(2-methylpropyl)-, [2S-[N4(R\*), 2R\*, 3S\*]]-,

-264-

10)

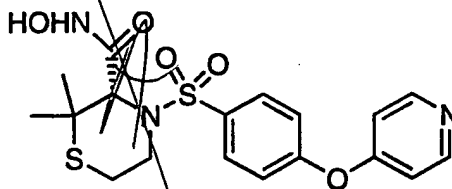


Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-  
iphenyl]-4-yl)oxy]-2-

5

[(phenylthio)methyl]butanoic acid,

11)



Agouron Pharmaceuticals AG-3340, N-hydroxy-2,2  
dimethyl-4-[[4-(4-  
pyridinyloxy)phenyl]sulfonyl] 3-  
thiomorpholinecarboxamide,

10

12) CollaGenex Pharmaceuticals CMT-3 (Metastat),  
6-demethyl-6-deoxy-4-

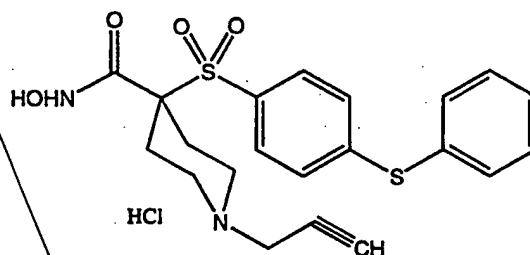
15

dedimethylaminotetracycline,

13) Chiroscience D-2163, 2- [1S- ([ (2R,S)-  
acetylmercapto- 5- phthalimido]pentanoyl- L-  
leucyl)amino- 3- methylbutyl]imidazole,

-265-

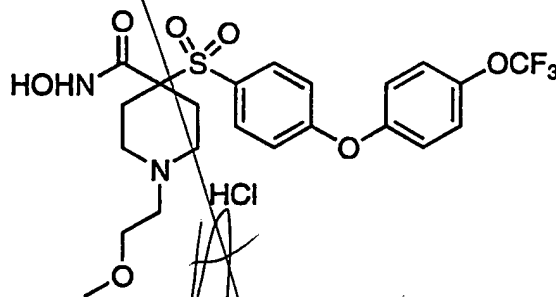
14)



N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-  
1-(2-propynyl)-4-piperidinecarboxamide  
monohydrochloride,

5

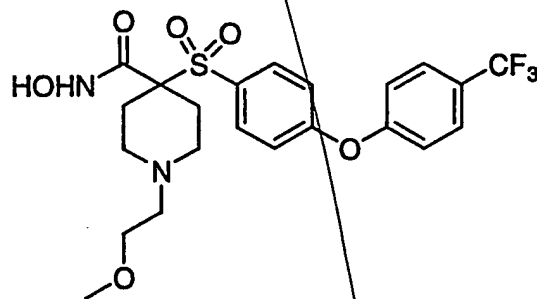
15)



N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-  
(trifluoromethoxy) phenoxy]phenyl]sulfonyl]-4-  
piperidinecarboxamide monohydrochloride,

10

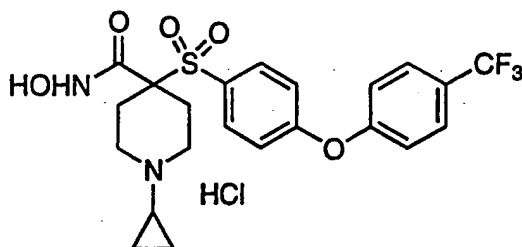
16)



N-hydroxy-1-(2-methoxyethyl)-4-[[4-[4-  
(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-  
piperidinecarboxamide,

15

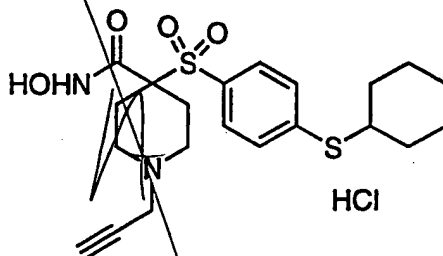
17)



1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride,

5

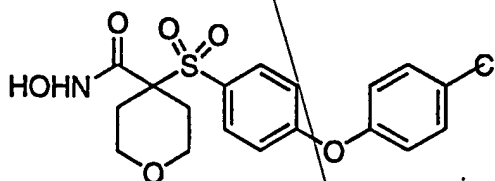
18)



4-[[4-(cyclohexylthio)phenyl]sulfonyl]-N-hydroxy-1-(2-propynyl)-4-piperidinecarboxamide monohydrochloride,

10

19)

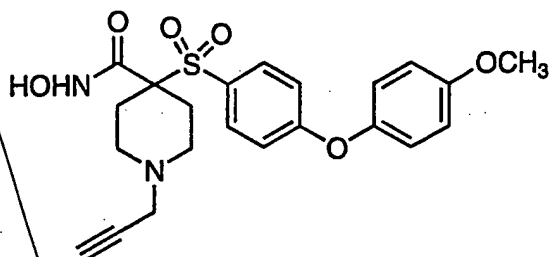


15

4-[[4-(4-chlorophenoxy)phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide,

-267-

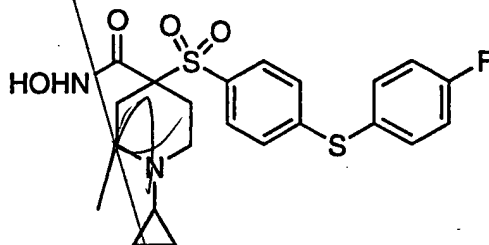
20)



N-hydroxy-4-[[4-(4-methoxyphenoxy)phenyl]sulfonyl]-1-(2-propynyl)-4-piperidinecarboxamide,

5

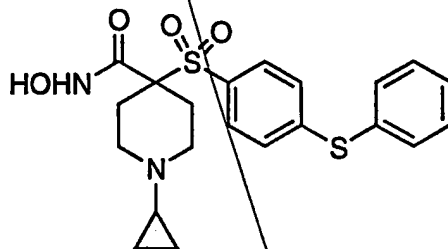
21)



1-cyclopropyl-4-[[4-(4-fluorophenyl)thio]phenyl]sulfonyl]-N-hydroxy-4-piperidinecarboxamide,

10

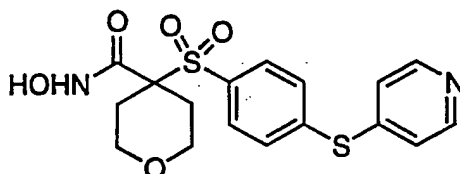
22)



1-cyclopropyl-N-hydroxy-4-[[4-(phenylthio)phenyl]sulfonyl]-4-piperidinecarboxamide,

15

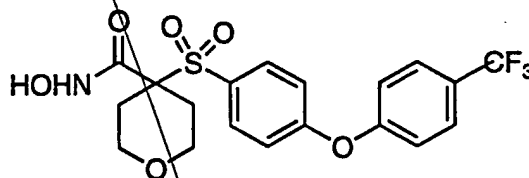
23)



tetrahydro-N-hydroxy-4-[[4-(4-pyridinylthio)phenyl]sulfonyl]-2H-pyran-4-carboxamide, and

5

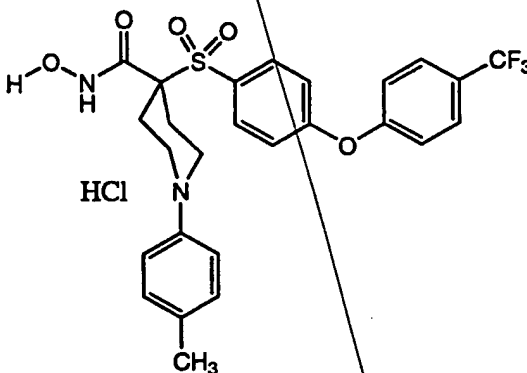
24)



tetrahydro-N-hydroxy-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide.

10

89. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is

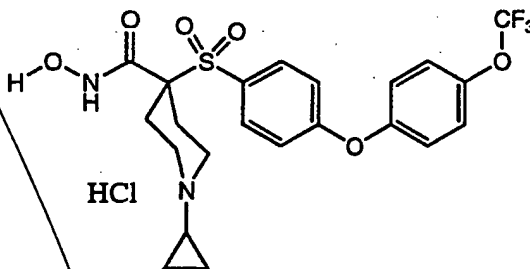


N-hydroxy-1-(4-methylphenyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

15

-269-

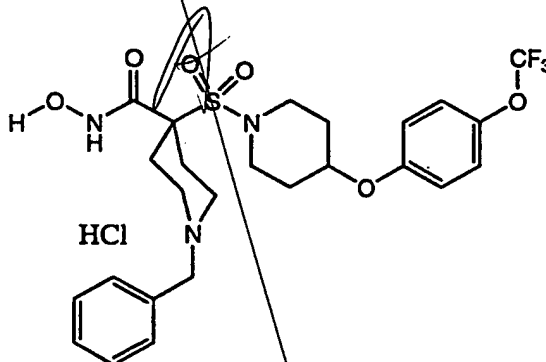
90. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is



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1-cyclopropyl-N-hydroxy-4-[[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

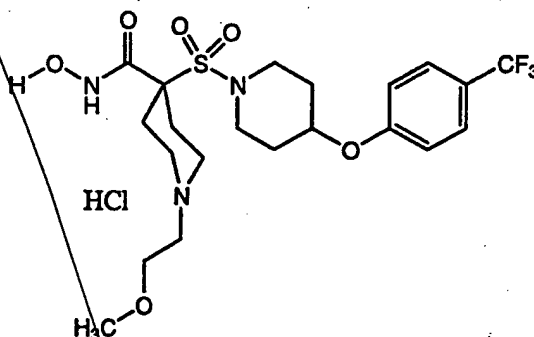
91. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is



10

N-hydroxy-1-(phenylmethyl)-4-[[4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

92. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is

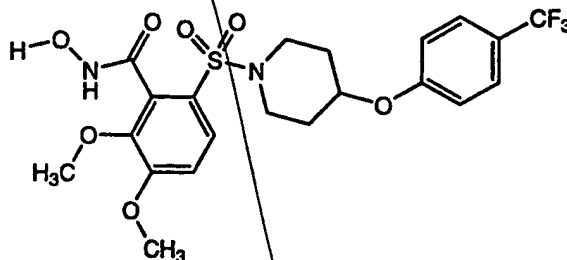


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N-hydroxy-1-(4-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide dihydrochloride.

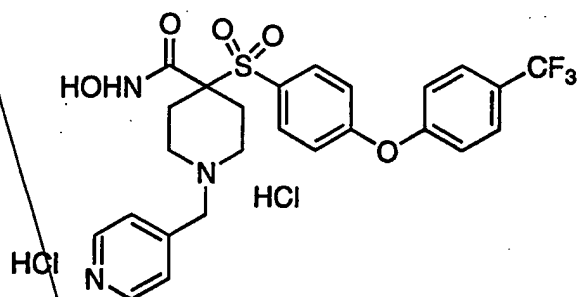
93. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is

10

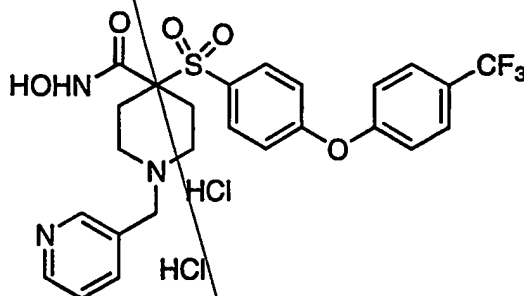


N-hydroxy-2,3-dimethoxy-6-[[4-[4-(trifluoromethyl)phenoxy]-1-piperidinyl]sulfonyl]benzamide.



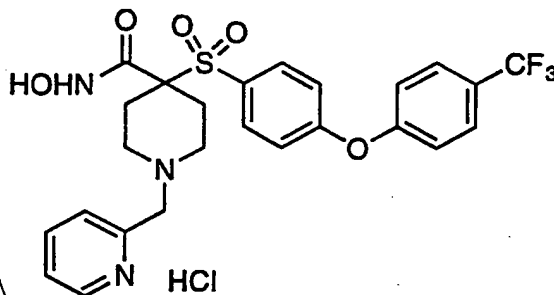


95. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is



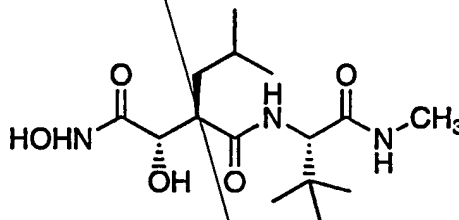
15 piperidinecarboxamide dihydrochloride.

96. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is



N-hydroxy-1-(2-pyridinylmethyl)-4-[[4-[4-(trifluoromethyl)phenoxy]phenyl]sulfonyl]-4-piperidinecarboxamide monohydrochloride.

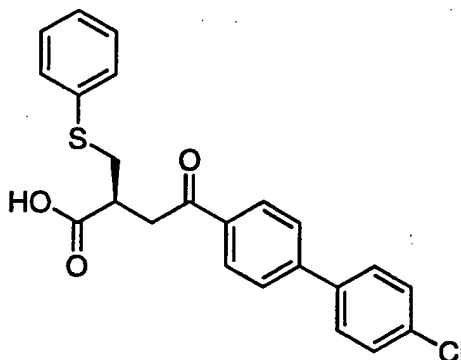
97. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is



British Biotech BB-2516 (Marimastat), N4-[2,2-dimethyl-1-[(methylamino)carbonyl]propyl]-N1,2-dihydroxy-3 (2-methylpropyl)-, [2S-[N4(R\*),2R\*,3S\*]]-.

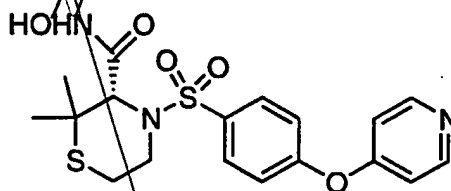
-273-

99. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is



5 Bayer Ag Bay-12-9566, 4-[(4'-chloro[1,1'-  
iphenyl]-4-yl)oxy]-2-  
[(phenylthio)methyl]butanoic acid.

100. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is



15 Agouron Pharmaceuticals AG-3340, N-hydroxy-  
2,2-dimethyl-4-[[4-(4-  
pyridinyloxy)phenyl]sulfonyl]-3-  
thiomorpholinecarboxamide.

101. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is CollaGenex  
Pharmaceuticals CMT-3 (Metastat), 6-demethyl-6-deoxy-4-  
20 dedimethylaminotetracycline.

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102. The combination of Claim 87 wherein the matrix metalloproteinase inhibitor is Chiroscience D-2163, 2-[1S- ((2R,S)- acetylmercapto- 5- phthalimido]pentanoyl-L- leucyl)amino- 3- methylbutyl]imidazole.

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103. The method of Claim 1 wherein the antineoplastic agent is anastrozole.

104. The method of Claim 1 wherein the  
10 antineoplastic agent is calcium carbonate.

105. The method of Claim 44 wherein the antineoplastic agent is anastrozole.

15 106. The method of Claim 44 wherein the antineoplastic agent is calcium carbonate.

add  
A4